

### REMARKS

Claims 1-3, 6-9 and 11-27 are active in the present application.

Applicants wish to thank Examiner Kerr for the indication that Claims 8, 9, and 11-16 are free of the art of record (December 17, Office Action, page 7, paragraph 17).

In view of the amendments submitted herein and the following remarks, favorable reconsideration and allowance of all pending claims is requested.

The rejection of Claims 1-3, 6-7, 18-24 and 26-27 under 35 U.S.C. §112, first paragraph (enablement), is traversed.

Although the Examiner concedes that the skilled artisan knows how to make and test mutants, the Examiner has maintained this ground of rejection alleging that the skilled artisan has not been enabled to reduce or eliminate PBP activity other than by deletion. However, Applicants remind the Examiner that MPEP § 2164.01 states:

The test of enablement is whether one reasonably skilled in the art could make or use the invention from the disclosures in the patent coupled with information known in the art without undue experimentation.

To evidence the general knowledge in the art and the ability of the skilled artisan to reduce or eliminate enzyme activity by more than deletion of a gene, Applicants **submit herewith** Valenski et al (*J.Bacteriol.*, 185, 5007-5011 (2003)). Valenski et al demonstrate that the expression of the *fimI* gene is prevented by introducing a frame-shift mutation thereby resulting in a reduction in the activity of the protein encoded by the *fimI* gene.

Therefore, for the reasons set forth in the Amendment and Request for Reconsideration filed on August 27, 2003 and further augmented by the knowledge in the art

(above), Applicants submit that the skilled artisan would readily appreciate methods for reducing or eliminating the function of a gene product, especially when the gene sequence is known, by modifying the gene by mutations beyond just deletion of the gene, such as by: substitution, insertion, addition, and/or inversion. Therefore, Applicants request withdrawal of this ground of rejection.

The rejection of Claims 2-3, 7, 21, 22, and 24 under 35 U.S.C. §112, second paragraph, is obviated by amendment.

Applicants submit that the claims have been amended to free of the Examiner's criticism. Specifically, Applicants note that Claim 2 has been amended to clarify the relationship between the first and second temperatures and the method of Claim 1 from which Claim 2 depends (*i.e.*, the first and second temperatures are steps in the cultivation step defined in Claim 1). In regard to Claim 3, Applicants have amended this claim based on the Examiner's helpful suggestion.

In view of the present amendments, withdrawal of this ground of rejection is requested.

The rejections of Claims 2 and 21 under 35 U.S.C. §112, first paragraph (written description and enablement), are obviated by amendment.

The Examiner has maintained the rejections of Claims 2 and 21 alleging that it is unclear what mutations of the PBP gene give rise to temperature sensitivity. Applicants note the Examiner appears to have misinterpreted these claims and the mutations thereof. As clearly defined in the claims, the temperature sensitivity arises due to "the expression of the functioning penicillin binding protein is under the control of a temperature sensitive

replicon". In this regard, the Examiner's attention is drawn to pages 20-22 of the specification, which clearly sets forth and defines temperature sensitive replicons, methods for obtaining these replicons, and use thereof.

For sake of clarity, Applicants direct the Examiner's attention to Claim 1 (from which Claims 2 and 21 depend), which clearly describes the nature of the mutation of the chromosomal PBP gene. Specifically, Claim 1 defines the mutation of the chromosomal penicillin binding protein gene stating:

"mutating all or a portion of a chromosomal gene of a penicillin binding protein 3 in a coryneform bacteria such that the penicillin binding protein 3 encoded by the chromosomal gene of the penicillin binding protein 3 is not produced or the function of the penicillin binding protein 3 encoded by the chromosomal gene of the penicillin binding protein 3 is reduced or eliminated in said coryneform bacteria..."

Therefore, as the skilled artisan would readily appreciate, the mutation of the chromosomal penicillin binding protein serves to reduce or eliminate activity of the enzyme and not to induce temperature sensitivity.

In view of the foregoing, Applicants submit that Claims 2 and 21 (i.e., the origin of the temperature sensitivity) is fully described and enabled. Accordingly, Applicants request withdrawal of these grounds of rejection.

The rejection of Claims 1-3, 6, 7, and 17-27 under 35 U.S.C. §112, second paragraph, is obviated by amendment.

The Examiner has rejected the claims as being indefinite alleging that the claims do not specify which of the penicillin binding proteins of coryneform bacteria are mutated. Applicants note that the claims have been amended to define the penicillin binding protein as

the penicillin binding protein 3 (PBP3). Therefore, Applicants submit that the claims are clear as to which penicillin binding protein is claimed.

In regard to the terms native, non-native, functioning, and non-functioning, Applicants note that native and non-native do not appear in the claims. Nonetheless, the meanings of these terms can be ascertained from the specification in that the term “native” refers to the endogenous wild-type penicillin binding protein, while the non-native refers to any other penicillin binding protein gene.

As disclosed in the specification (for example on pages 8-11) the native PBP gene on the chromosome has one or mutations such that the PBP is not produced or the function (activity) of the PBP is reduced or eliminated. Thus the chromosomal copy of the PBP gene is “non-functioning.” So long as the PBP gene on the chromosome is non-functioning either a native PBP gene or a non-native PBP gene can be used for the present invention. The “functioning” (active) copy of the PBP gene on the plasmid is a non-native PBP gene.

Applicants request withdrawal of this ground of rejection.

Applicants submit that the present application is now in condition for allowance.

Early notification of such action is earnestly solicited.

Respectfully submitted,

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